

Tokujiro Uchida  
Kuninori Yokoyama  
Koichi Nakazawa  
Koshi Makita

## Partial pressure of oxygen and partial pressure of carbon dioxide of perfluorocarbon liquid during partial liquid ventilation: their regional difference and their dependence on tidal volume and positive end-expiratory pressure level

Received: 29 February 2000  
Final revision received: 10 July 2000  
Accepted: 31 August 2000  
Published online: 5 January 2001  
© Springer-Verlag 2001

This study was supported by grants in aid from the ministry of education, science and culture, Japan.

This study was partially presented at the 1999 Annual Meeting of the American Society of Anesthesiologists on October 12, 1999, in Dallas, Texas, USA.

T. Uchida (✉) · K. Yokoyama ·  
K. Nakazawa · K. Makita

Department of Anesthesiology and Critical Care Medicine, Tokyo Medical and Dental University, School of Medicine, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan  
E-mail: uchida.mane@tmd.ac.jp  
Phone: +81-3-5803 5325  
Fax: +81-3-5803 0150

**Abstract** *Objective:* To investigate the regional partial pressure of oxygen ( $PO_2$ ) and partial pressure of carbon dioxide ( $PCO_2$ ) of the perfluorocarbon liquid ( $PpfcO_2$ ,  $PpfcCO_2$ ) during partial liquid ventilation (PLV).

*Design:* Prospective, controlled study.

*Setting:* A research laboratory at a university medical center.

*Subjects:* Thirteen Japanese white rabbits.

*Interventions:* After the tracheostomy, PLV was started with perflubron (15 ml/kg) following saline lung lavage. Fractional inspired oxygen ( $FIO_2$ ) was 1.0, respiratory rate was 30 bpm and tidal volume ( $V_T$ ) was 30 ml. Two epidural catheters (18 gauge) were inserted from the rubber diaphragm interposed in the respiratory circuit to sample perflubron. One catheter was inserted into the left lower lobe bronchus and placed at 5–6 cm distal from the carina (DISTAL). The other one was inserted at the tip of the endotracheal tube (PROXIMAL). Then the effect of the larger  $V_T$  (50 ml) or positive end-expiratory pressure (PEEP; 10 cmH<sub>2</sub>O) to the

gas tension in perflubron was examined.

*Measurements and main results:* (1) In the lower  $V_T$  (30 ml) with 0 cmH<sub>2</sub>O PEEP, DISTAL  $PpfcO_2$  was significantly lower than PROXIMAL  $PpfcO_2$  ( $265 \pm 72$  vs  $386 \pm 47$  mmHg,  $p < 0.0001$ ), and DISTAL  $PpfcCO_2$  was significantly higher than PROXIMAL  $PpfcCO_2$  ( $51.1 \pm 14.4$  vs  $42.4 \pm 11.8$  mmHg ( $p = 0.0007$ )), (2) the higher  $V_T$  setting increased  $PpfcO_2$  ( $p = 0.0001$ ) and decreased  $PpfcCO_2$  ( $p < 0.0001$ ), although the gas tension gradient was significant, (3) 10 cmH<sub>2</sub>O PEEP increased  $PpfcO_2$  ( $p = 0.0004$ ) and decreased  $PpfcCO_2$  ( $p = 0.0089$ ) in the DISTAL sample.

*Conclusion:* There was a difference in gas tension in perflubron between the central airway and the peripheral dependent lung region, and gas tension in perflubron was affected by the  $V_T$  and the PEEP level.

**Key words** Liquid ventilation · Perflubron · Partial pressure of oxygen ( $PO_2$ ) · Partial pressure of carbon dioxide ( $PCO_2$ ) · Positive end-expiratory pressure (PEEP) · Tidal volume

### Introduction

Partial liquid ventilation (PLV) is a ventilatory method performed by conventional gas ventilation to the perfluorocarbon (PFC) liquid instilled lung. Since this method

was first reported by Fuhrman et al. [1], both animal research and clinical trials have demonstrated its therapeutic potential in cases of severe lung injury [2, 3, 4, 5, 6, 7]. From the viewpoint of pulmonary gas exchange, most of the discussions in the previous reports have

been based on arterial blood gas analyses. However, partial pressures of  $O_2$  (P<sub>pfc</sub> $O_2$ ) and  $CO_2$  (P<sub>pfc</sub> $CO_2$ ) have not been elucidated yet.

During PLV, the mechanism of pulmonary gas exchange is complex because both gas and PFC liquid take part in it. In addition, both oxygenation and  $CO_2$  removal are accomplished in the lung *in situ*. The efficiency of gas exchange is affected by the gas diffusion within the liquid and amount of gas-liquid interface. However, Mates et al. concluded that the diffusion limitation in the PFC liquid was less important for oxygenation and PFC-flooded gas exchange units, which the fresh inspiratory gas could not reach throughout the respiratory cycle, caused intrapulmonary shunt [8]. Recently, we demonstrated that airway pressure above the lower inflection point on the pressure-volume curve established the gas-liquid interface dose dependently from the non-dependent lung region during PLV [9]. Furthermore, severe lung injury with low lung compliance made it difficult to establish gas-liquid interface in the dependent lung region even during PLV. Considering these studies, we hypothesized that (1) P<sub>pfc</sub> $O_2$  was inhomogeneous in the lung *in situ* and it is lower in the dependent lung region than in the proximal airway, (2) P<sub>pfc</sub> $O_2$  was determined not only by the FIO<sub>2</sub> but also by the setting of supplemental gas ventilation during PLV.

The first objective of this study, therefore, was to determine whether P<sub>pfc</sub> $O_2$  in the dependent region of injured lung was lower than that in the central airway. The second objective was to determine whether the higher tidal volume (V<sub>T</sub>) increased P<sub>pfc</sub> $O_2$ , and whether the higher V<sub>T</sub> decreased the regional difference of P<sub>pfc</sub> $O_2$  between the central airway and the peripheral dependent region. Finally, the third objective was to determine whether PEEP increased P<sub>pfc</sub> $O_2$  in the peripheral dependent region.

## Materials and methods

The following protocol was approved by the institutional animal ethics committee. All animals were handled according to the guidelines set out in the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health.

Thirteen Japanese white rabbits (2.7–3.4 kg) were anesthetized with intramuscular ketamine (100 mg) and xylazine (12.5 mg). After establishing a venous route via the marginal ear vein, tracheostomy was established under local anesthesia and an endotracheal tube (internal diameter, 4.0 mm) (Lo-contour; Mallincrodt Medical, Athlone, Ireland) was inserted. Ketamine (10 mg), xylazine (12.5 mg) and pancuronium (1.0 mg) were administered intravenously and volume-controlled mechanical ventilation was started with an animal ventilator (SN-480-6; Shinano, Tokyo, Japan). Tidal volume (V<sub>T</sub>) was set to 30 ml and respiratory rate was set to 30 breaths/min. The inspiratory-expiratory ratio (I:E) was set to 1:2, FIO<sub>2</sub> was 1.0, and 6 ml·kg<sup>-1</sup>·h of lactate Ringer's solution was continuously infused as a maintenance fluid. Anesthesia was main-

tained with continuous infusion of ketamine (10 mg/h), xylazine (25 mg/h) and pancuronium (1 mg/h). A central venous catheter was inserted via the right jugular vein and the right carotid artery was cannulated with a 20-gauge Teflon cannula (Surflow; Terumo, Tokyo, Japan). Esophageal temperature was continuously monitored and adjusted within the range of 36.5–37.5°C throughout the experiment, using an infra-red radiation warmer.

### Study protocol

After the baseline measurements, the lungs were lavaged several times with 40 ml of normal saline at 37°C until PaO<sub>2</sub> decreased to less than 100 mmHg, using a modification of the technique described by Lachmann et al. [10]. After 1-h stabilization of lung injury, PLV was started with 15 ml/kg of perflubron (Perfluoroctylbromide C<sub>8</sub>F<sub>17</sub>Br; PFOB, Nippon Mektron, Tokyo, Japan). The specific gravity of this liquid is 1.92 at 25°C; vapor pressure is 14.0 mmHg at 37°C. To evaluate oxygenation of perflubron in the lung *in situ*, it was instilled without pre-oxygenation. In addition, the lung was ventilated with 100% oxygen every 3 ml of instillation without any change in body position. Our previous study demonstrated this instillation method caused gravity dependent distribution of perflubron [9]. During PLV, respiratory rate (RR) was set to 30 breaths/min, FIO<sub>2</sub> was set to 1.0 and V<sub>T</sub> was set to 30 ml. Then two epidural catheters (18 gauge Epidural Minipack, SIMS Portex, Kent, UK) were inserted from the rubber diaphragm interposed in the respiratory circuit, to sample perflubron. One catheter, defined as a DISTAL catheter, was inserted into the left lower lobe bronchus with fiberoptic guidance and placed at a point 5–6 cm distal of the carina. And the other catheter, defined as a PROXIMAL catheter, was inserted at the tip of the endotracheal tube.

One hour after the PFC sampling catheters had been inserted, the experimental protocol was started. The protocol consisted of the three different settings of supplemental gas ventilation in random sequence: the first setting was the lower V<sub>T</sub> (30 ml) with 0 cmH<sub>2</sub>O PEEP (ZEEP), the second setting was the higher V<sub>T</sub> (50 ml) with ZEEP, and the third setting was the lower V<sub>T</sub> (30 ml) with 10 cmH<sub>2</sub>O PEEP. At all settings RR was 30 breaths/min and FIO<sub>2</sub> was 1.0. Each setting of ventilation was continued for 45 min and measurements were performed at the end of each cycle.

After all the measurements had been completed, animals were exsanguinated under deep pentobarbital anesthesia and the chest was opened with midsternal incision to examine the location of the catheter. When the distal catheter was inserted into the bronchus other than the ramus laterobasalis (B<sup>9</sup>) or the ramus dorsobasalis (B<sup>10</sup>), the results were excluded from the study.

### Measurements

Mean arterial pressure (MAP) was continuously monitored using a monitoring system (Lifescope 12, Nihonkohden, Tokyo, Japan). Arterial blood was sampled and analyzed using a blood gas analyzer (IL1306A; Instrumentation Laboratory, Milan, Italy). Perflubron (0.2 ml each) was sampled from the DISTAL and PROXIMAL catheters, after withdrawal of perflubron from within the epidural tube dead space (approximately 0.25 ml), during a temporary cessation of ventilation at the end expiratory phase. In the setting of lower V<sub>T</sub> with 10 cmH<sub>2</sub>O PEEP, PEEP was decreased to 0 cmH<sub>2</sub>O during this period to facilitate sampling. In the setting with 10 cmH<sub>2</sub>O PEEP, PROXIMAL samples were excluded from analyses because PROXIMAL airways were occupied with gas during the ventilation with PEEP. Both P<sub>pfc</sub> $O_2$  and P<sub>pfc</sub> $CO_2$  were

**Table 1** Airway pressure and hemodynamic variables ( $V_T$  tidal volume, ZEEP 0 cmH<sub>2</sub>O positive end-expiratory pressure, PEEP positive end-expiratory pressure, PIP peak inspiratory pressure, HR heart rate, MAP mean arterial pressure)

	$V_T$ 30 ml + ZEEP	$V_T$ 50 ml + ZEEP	$V_T$ 30 ml + 10 cmH <sub>2</sub> O PEEP
PIP (cmH <sub>2</sub> O)	14 ± 3	21 ± 3**	20 ± 3**
HR (beats/min)	205 ± 42	225 ± 43	214 ± 42
MAP (mmHg)	96 ± 10	86 ± 13*	85 ± 15*

Data are shown as mean ± SD

\*  $p < 0.05$  vs  $V_T$  30 ml + ZEEP, \*\*  $p < 0.0001$  vs  $V_T$  30 ml + ZEEP

analyzed using the blood gas analyzer at 37 °C by the same method as arterial blood samples. The dose equivalent to the loss of perflubron by each sampling was refilled into the endotracheal tube after each measurement.

#### Statistics

All data are expressed as means ± SD. All statistical analyses were performed with computer software (Stat View 4.5; Abacus Concepts, Berkeley, Calif.). The effect of the sampling site and  $V_T$  to PpfcO<sub>2</sub> and PpfcCO<sub>2</sub> were analyzed with two-way analyses of variance (ANOVA). To compare the variables from the two different ventilatory settings, paired *t*-test was performed. The level of significance was a probability of 0.05 or less in each statistical analysis.

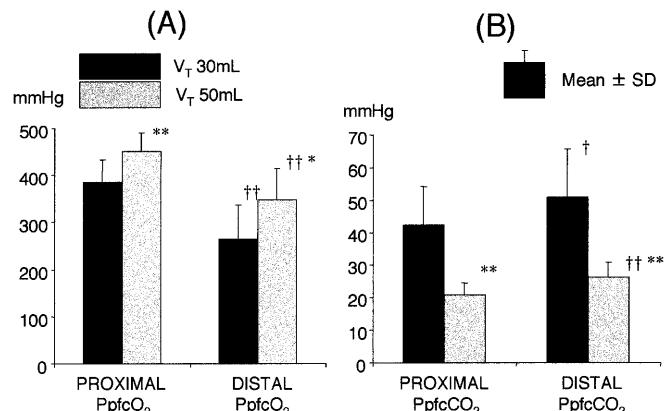
#### Results

As a preliminary study, we evaluated applicability of the blood gas analyzer to measurements of PpfcO<sub>2</sub> and PpfcCO<sub>2</sub>. The accuracy for PFC samples was comparable with that for blood samples warranted by the manufacturer (Data not shown). Two of 13 animals were excluded because of catheter malpositioning. In these two animals, the DISTAL catheter was inserted into the ramus ventrobasalis (B<sup>8</sup>). In the 11 animals studied, the location of the DISTAL catheter was in the ramus laterobasalis (7 animals), or in the ramus dorsobasalis (4 animals).

Peak inspiratory pressure (PIP), heart rate (HR) and mean arterial pressure (MAP) in the three ventilatory settings are demonstrated in Table 1. Both higher  $V_T$  and PEEP significantly decreased MAP; however, no animal recorded severe hypotension (MAP < 60 mmHg) during the experiment.

Regional difference of partial pressures of oxygen and carbon dioxide of the perfluorocarbon liquid during partial liquid ventilation

In the lower  $V_T$  (30ml) with ZEEP, DISTAL PpfcO<sub>2</sub> was significantly lower than PROXIMAL PpfcO<sub>2</sub> (265 ± 72



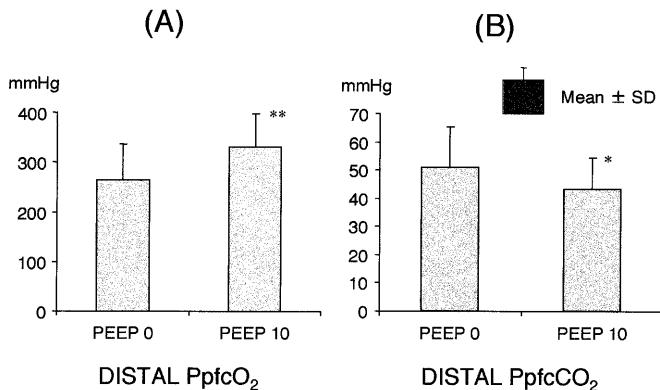
**Fig. 1** Effect of tidal volume ( $V_T$ ) setting to the gas tension in perflubron during partial liquid ventilation. (A) Partial pressure of oxygen of perfluorocarbon liquid (B) Partial pressure of carbon dioxide of perfluorocarbon liquid; \*  $p = 0.0001$  vs  $V_T$  30 ml, \*\*  $p < 0.0001$  vs  $V_T$  30 ml, †  $p < 0.001$  vs PROXIMAL sample, ††  $p < 0.0001$  vs PROXIMAL sample

vs 386 ± 47 mmHg,  $p < 0.0001$ ), and DISTAL PpfcCO<sub>2</sub> was significantly higher than PROXIMAL PpfcCO<sub>2</sub> (51.1 ± 14.4 vs 42.4 ± 11.8 mmHg, ( $p = 0.0007$ )).

#### Effect of tidal volume setting on the partial pressures of oxygen and carbon dioxide of the perfluorocarbon liquid during partial liquid ventilation

The result of comparison of PpfcO<sub>2</sub> between the two  $V_T$  settings (30ml or 50 ml) with ZEEP is demonstrated in Fig. 1A. The result of two-way ANOVA demonstrated that both sampling sites ( $p < 0.0001$ ), and  $V_T$  settings ( $p < 0.0001$ ) significantly affected PpfcO<sub>2</sub>. The higher  $V_T$  setting resulted in the higher PpfcO<sub>2</sub> (451 ± 39 [V<sub>T</sub> 50 ml] vs 386 ± 47 mmHg [V<sub>T</sub> 30 ml] in the PROXIMAL sample ( $p < 0.0001$ ); 347 ± 68 [V<sub>T</sub> 50 ml] vs 265 ± 72 mmHg [V<sub>T</sub> 30 ml] in the DISTAL sample,  $p = 0.0001$ ). In addition, the regional difference of PpfcO<sub>2</sub> was significant in the higher  $V_T$  setting (451 ± 39 [PROXIMAL] vs 347 ± 68 mmHg [DISTAL],  $p < 0.0001$ ).

The result of comparison of PpfcCO<sub>2</sub> between the two  $V_T$  settings with ZEEP is demonstrated in Fig. 1B. The result of two-way ANOVA demonstrated that sampling sites ( $p = 0.02$ ), and  $V_T$  settings ( $p < 0.0001$ ) significantly affected PpfcCO<sub>2</sub>. The higher  $V_T$  setting resulted in the lower PpfcCO<sub>2</sub> (20.8 ± 3.8 [V<sub>T</sub> 50 ml] vs 42.4 ± 11.8 mmHg [V<sub>T</sub> 30 ml] in the PROXIMAL sample ( $p < 0.0001$ ); 26.4 ± 4.4 [V<sub>T</sub> 50 ml] vs 51.1 ± 14.4 mmHg [V<sub>T</sub> 30 ml] in the DISTAL sample;  $p < 0.0001$ ). In addition, the regional difference of PpfcCO<sub>2</sub> was significant in the higher  $V_T$  setting (20.8 ± 3.8 [PROXIMAL] vs 26.4 ± 4.4 mmHg [DISTAL];  $p < 0.0001$ ).



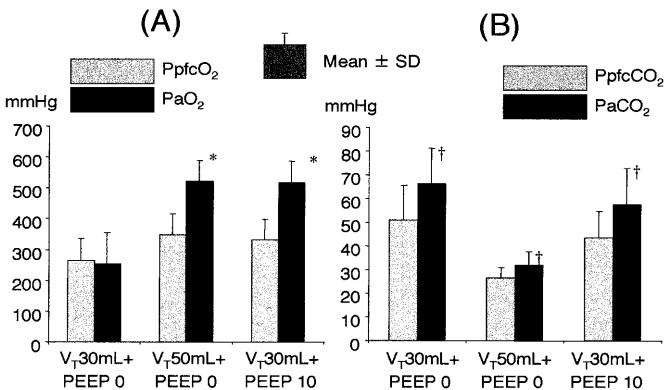
**Fig. 2** Effect of 10 cmH<sub>2</sub>O positive end-expiratory pressure (PEEP) to the gas tension in the DISTAL perflubron samples during partial liquid ventilation. (A) Partial pressure of oxygen of perfluorocarbon liquid (B) Partial pressure of carbon dioxide of perfluorocarbon liquid (PEEP 0 0 cmH<sub>2</sub>O PEEP, PEEP 10: 10 cmH<sub>2</sub>O PEEP) \*  $p < 0.01$  vs PEEP 0, \*\*  $p < 0.001$  vs PEEP 0

Effect of positive end-expiratory pressure on the DISTAL partial pressures of oxygen and carbon dioxide of perfluorocarbon liquid during partial liquid ventilation

The result of comparison of gas tension in the DISTAL samples between the lower V<sub>T</sub> with ZEEP and the lower V<sub>T</sub> with 10cmH<sub>2</sub>O PEEP is demonstrated in Fig. 2. PEEP significantly increased DISTAL PpfcO<sub>2</sub> (265 ± 72 [ZEEP] vs 331 ± 67 mmHg [10 cmH<sub>2</sub>O PEEP],  $p = 0.0004$ ; Fig. 2A), and significantly decreased PpfcCO<sub>2</sub> (57.6 ± 15.3 [ZEEP] vs 43.5 ± 11.1 mmHg [10 cmH<sub>2</sub>O PEEP],  $p = 0.0089$ ; Fig. 2B).

The gas tension difference between the DISTAL perflubron samples and the arterial samples

Figure 3 shows the partial pressure difference between the arterial and the DISTAL perflubron samples. Although PO<sub>2</sub> difference was not significant in the setting of lower V<sub>T</sub> with ZEEP (265 ± 72 [DISTAL PpfcO<sub>2</sub>] vs 252 ± 103 mmHg [PaO<sub>2</sub>]  $p = 0.7287$ ), higher V<sub>T</sub> and PEEP resulted in a significant PO<sub>2</sub> difference between the arterial and perflubron samples (347 ± 68 [DISTAL PpfcO<sub>2</sub>] vs 521 ± 69 mmHg [PaO<sub>2</sub>] ( $p < 0.0001$ ) in the higher V<sub>T</sub> setting, 331 ± 67 [DISTAL PpfcO<sub>2</sub>] vs 516 ± 69 mmHg [PaO<sub>2</sub>] ( $p < 0.0001$ ) in the PEEP setting; Fig. 3A). On the other hand, the PCO<sub>2</sub> difference was significant in all the three settings (51.1 ± 14.4 [DISTAL PpfcCO<sub>2</sub>] vs 66.1 ± 15.1 mmHg [PaCO<sub>2</sub>] ( $p = 0.0002$ ) in the lower V<sub>T</sub> with ZEEP, 26.4 ± 4.4 [DISTAL PpfcCO<sub>2</sub>] vs 31.8 ± 5.7 mmHg [PaCO<sub>2</sub>] ( $p = 0.0002$ ) in the higher V<sub>T</sub> with ZEEP, 43.5 ± 11.1 [DISTAL PpfcCO<sub>2</sub>] vs 57.6 ± 15.3 mmHg [PaCO<sub>2</sub>]



**Fig. 3** The gas tension difference between the arterial samples and the DISTAL perflubron samples. (A) Oxygen (B) Carbon dioxide (PEEP 0 0 cmH<sub>2</sub>O PEEP, PEEP 10 10 cmH<sub>2</sub>O PEEP) \*  $p < 0.0001$  vs PpfcO<sub>2</sub>, †  $p < 0.001$  vs PpfcCO<sub>2</sub>

( $p = 0.0005$ ) in the lower V<sub>T</sub> with 10 cmH<sub>2</sub>O PEEP; Fig. 3B).

## Discussion

The present study has demonstrated that (1) there was a difference in gas tension in perflubron between the central airway and the dependent lung region, (2) a higher V<sub>T</sub> setting increased PpfcO<sub>2</sub> and decreased PpfcCO<sub>2</sub> during PLV, although the gas tension gradient was significant, (3) 10 cmH<sub>2</sub>O PEEP increased PpfcO<sub>2</sub> and decreased PpfcCO<sub>2</sub> in the dependent lung region and (4) both higher V<sub>T</sub> and PEEP further increased PaO<sub>2</sub> compared to PpfcO<sub>2</sub> in the dependent lung region.

There are four types of alveolar filling status during PLV. The first type is alveolus filled with gas throughout the respiratory cycle (gas-filled alveolus) and the second one is alveolus where both gas and PFC liquid exist (gas-liquid-filled alveolus). The third type is alveolus flooded with PFC liquid throughout the respiratory cycle (liquid-filled alveolus) and the last one is collapsed alveolus.

## Oxygen in the perfluorocarbon liquid during partial liquid ventilation

Thinking about the oxygenation of PFC liquid, two types of alveoli, gas-liquid-filled alveoli and liquid-filled alveoli, should be considered. In the gas-liquid-filled alveoli, oxygen is supplied from inspiratory gas. On the other hand, in the liquid-filled alveoli the source of oxygen supply is limited to oxygen diffusion via the liquid.

Considering alveolar gas-capillary  $\text{PO}_2$  gradient during PLV, Mates et al. concluded, with a mathematical model, that diffusion limitation did not significantly contribute to the alveolar-arterial  $\text{O}_2$  gradient in the gas-liquid-filled alveoli [8]. In this situation,  $\text{PpfcO}_2$  could be equilibrated with both  $\text{PAO}_2$  and alveolar capillary  $\text{PO}_2$ . On the other hand, they calculated that a PFC-flooded gas exchange unit acts like a shunt when the gas radius is less than 50  $\mu\text{m}$  in the lung instilled with perflubron (30 ml/kg) [8]. In this situation,  $\text{PpfcO}_2$  could be equilibrated with mixed venous oxygen tension.

In addition, our previous study demonstrated that the gas is predominantly distributed to the non-dependent regions, and liquid-flooded alveoli can exist especially in the dependent regions in the injured lung [9]. Furthermore, increasing airway pressure resulted in the establishment of air-liquid interface from the non-dependent region dose dependently. Therefore we hypothesized that the number of liquid-flooded alveoli affected  $\text{PpfcO}_2$ .

Our present study supported this hypothesis by the following two points. Firstly,  $\text{PpfcO}_2$  in the DISTAL samples were significantly lower than that in the PROXIMAL samples. This result was evidence of the existence of liquid-flooded alveoli in the DISTAL area in the dependent lung, which corresponded to  $\text{B}^9$  or  $\text{B}^{10}$ , regardless of the  $\text{V}_T$  settings. Secondly,  $\text{PpfcO}_2$  was increased by the higher  $\text{V}_T$  setting or 10  $\text{cmH}_2\text{O}$  PEEP. This result reflected the increase in the number of gas-liquid-filled alveoli by  $\text{V}_T$  increment or PEEP, which resulted in improvement of mixing status between inspiratory gas and perflubron. Several previous reports demonstrated that higher  $\text{V}_T$  [11] or PEEP [12] caused higher  $\text{PaO}_2$ . Those improvements in  $\text{PaO}_2$  could be partially explained by the decrease in the number of liquid-flooded alveoli caused by the higher  $\text{V}_T$  setting or PEEP.

#### Carbon dioxide in the perfluorocarbon liquid during partial liquid ventilation

In our present study we have demonstrated that (1) there was a regional difference in  $\text{PpfcCO}_2$  between the PROXIMAL and the DISTAL samples and  $\text{PaCO}_2$  was higher than the DISTAL  $\text{PpfcCO}_2$ , (2) PEEP (without any change in  $\text{V}_T$  and RR) reduced the DISTAL  $\text{PpfcCO}_2$ .

Partial pressure of carbon dioxide of perfluorocarbon fluid was determined by the relationship among the alveolar capillary perfusion, gas ventilation and  $\text{CO}_2$  diffusion within the liquid. The difference between  $\text{PaCO}_2$  and  $\text{PpfcCO}_2$  could be explained by the existence of ventilation dead space and alveolar-capillary  $\text{CO}_2$  diffusion limitation. At the level of the alveolar capillary barrier, the  $\text{CO}_2$  diffusion is limited between blood and PFC liq-

uid because of the relative insolubility of  $\text{CO}_2$  in perflubron ( $0.256 \text{ ml} \times 100 \text{ ml PFC}^{-1} \times 100 \text{ mmHg}^{-1}$ ) compared with in blood ( $0.779 \text{ ml} \times 100 \text{ ml blood}^{-1} \times 100 \text{ mmHg}^{-1}$ ) [8]. When 30 ml/kg of perflubron is used, the alveolar capillary-gas  $\text{PCO}_2$  gradient is as much as 10 mmHg in an average gas exchange unit, according to the calculation by Mate et al. [8]. This diffusion limitation could contribute to the difference between  $\text{PaCO}_2$  and  $\text{PpfcCO}_2$ , as well as ventilation dead space.

The regional difference of  $\text{PpfcCO}_2$  could be explained by the balance between the  $\text{CO}_2$  removal by the gas ventilation and the  $\text{CO}_2$  supply from alveolar capillary blood. In the PROXIMAL region, the contact between perflubron and alveolar capillary blood was less and  $\text{CO}_2$  was removed effectively by gas ventilation. In contrast, in the DISTAL region the gas-liquid interface was less established, so that  $\text{CO}_2$  removal was less effective compared with the PROXIMAL region. The effect of PEEP on the DISTAL  $\text{PpfcCO}_2$  could be explained by the theory that PEEP increased gas-liquid interface, which resulted in an increase in  $\text{CO}_2$  removal.

The relationship between partial pressure of oxygen of perfluorocarbon liquid and partial pressure of arterial oxygen

The results in this study demonstrated that both higher  $\text{V}_T$  and PEEP further increased  $\text{PaO}_2$  compared to  $\text{PpfcO}_2$  in the peripheral dependent lung region, which resulted in the significant difference between  $\text{PaO}_2$  and  $\text{PpfcO}_2$ . Furthermore,  $\text{PaO}_2$  was significantly higher than the PROXIMAL  $\text{PpfcO}_2$  in the higher  $\text{V}_T$  setting ( $521 \pm 69 \text{ [PaO}_2\text{]} \text{ vs } 451 \pm 39 \text{ mmHg [PROXIMAL PpfcO}_2\text{]}, p = 0.0070$ ). In these situations  $\text{PO}_2$  in the alveolar gas, rather than  $\text{PpfcO}_2$ , could be the dominant factor in determining  $\text{PaO}_2$ . In other words, improvement in the gas ventilation-perfusion matching increased  $\text{PaO}_2$ . PFC instillation would help alveolar recruitment by its lower surface tension and would induce inspiratory gas into those alveoli.

On the other hand, in the setting of lower  $\text{V}_T$  with ZEEP, there were no significant differences between  $\text{PaO}_2$  and DISTAL  $\text{PpfcO}_2$ . In this situation, perflubron might act like an oxygen reservoir and might play a major role in determining  $\text{PaO}_2$ . In addition, it was noteworthy that the true alveolar-arterial  $\text{PO}_2$  difference could not be evaluated with the alveolar gas equation, because peripheral  $\text{PpfcO}_2$  could be far lower than  $\text{PO}_2$  of inspiratory gas.

#### Study limitations

In this study, an epidural catheter was used to sample the DISTAL perflubron. Although the location of the

catheter was 5–6 cm distal from the carina, it was difficult to specify the anatomical region responsible for the DISTAL sample. In this sense, the sample was the mixture of perflubron from a more distal region than the segmental bronchus, which consisted of small bronchi, bronchioles and terminal alveolar sac. Therefore neither  $P_{pfc}O_2$  nor  $P_{pfc}CO_2$  in the terminal alveolar sac could be discussed in the present study. However, the significant difference between the PROXIMAL and the DISTAL samples reflected the regional difference in gas tension in perflubron and it suggested the possibility that  $P_{pfc}O_2$  in some terminal alveolar sac was lower than the DISTAL samples.

In addition, DISTAL samples in this study reflected the values in the perflubron exclusively in the dependent region. Because the mixing status between inspiratory gas and perflubron could be better in the non-dependent region,  $P_{pfc}O_2$  here could be higher than those

in the dependent regions. Because of the technical difficulty in introducing a catheter into the ventral region with reproducibility, this hypothesis could not be proved in the study. Therefore, the discussion should be limited to the relationship between the central airway and the peripheral dependent regions in this study. Finally, because the result of this study was based on a small animal experiment, our conclusion cannot be directly extrapolated to the human PLV. However, it should be considered that some settings of supplemental gas ventilation could result in lower  $P_{pfc}O_2$  in some regions and decrease efficiency in pulmonary gas exchange during PLV.

In conclusion, there was a difference in gas tension ( $P_{pfc}O_2$  and  $P_{pfc}CO_2$ ) in perflubron between the central airway and the dependent lung region, and gas tension in perflubron was affected by the  $V_T$  and the PEEP level.

## References

1. Fuhrman BP, Paczan PR, DeFrancisis M (1991) Perfluorocarbon-associated gas exchange. *Crit Care Med* 19: 712–722
2. Tutuncu AS, Faithful NS, Lachmann B (1993) Intratracheal perfluorocarbon administration combined with mechanical ventilation in experimental respiratory distress syndrome: dose-dependent improvement of gas exchange. *Crit Care Med* 21: 962–969
3. Leach CL, Fuhrmann BP, Morin FC III, Rath MG (1993) Perfluorocarbon-associated gas exchange (partial liquid ventilation) in respiratory distress syndrome: a prospective, randomized, controlled study. *Crit Care Med* 21: 1270–1278
4. Hirschl RB, Tooley R, Parent AC, Johnson K, Bartlett RH (1995) Improvement of gas exchange, pulmonary function and lung injury with partial liquid ventilation. A study model in a setting of severe respiratory failure. *Chest* 108: 500–508
5. Overbeck MC, Pranikoff T, Yadao CM, Hirschl RB (1996) Efficacy of perfluorocarbon partial liquid ventilation in a large animal model of acute respiratory failure. *Crit Care Med* 24: 1208–1214
6. Hirschl RB, Pranikoff T, Wise C, Overbeck MC, Gauger P, Schreiner RJ, Dechert R, Bartlett RH (1996) Initial experience with partial liquid ventilation in adult patients with the acute respiratory distress syndrome. *JAMA* 275: 383–389
7. Leach CL, Greenspan JS, Rubenstein SD, Shaffer TH, Wolfson MR, Jackson JC, DeLemos R, Fuhrman BP (1996) Partial liquid ventilation with perflubron in premature infants with severe respiratory distress syndrome. *N Engl J Med* 335: 761–767
8. Mates E, VanLobensels, Anderson JC, Hildebrandt J, Hlastala MP (1999) Modeling diffusion limitation of gas exchange in lungs containing perfluorocarbon. *J Appl Physiol* 86: 273–284
9. Uchida T, Makita K, Nakazawa K, Yokoyama K (2000) The relationship between airway pressure and distribution of gas-liquid interface during partial liquid ventilation in the oleic acid lung injury model: Fluorine-19 magnetic resonance imaging study. *Crit Care Med* 28: 2904–2908
10. Lachmann B, Robertson B, Vogel J (1980) In vivo lung lavage as an experimental model of the respiratory distress syndrome. *Acta Anesth Scand* 24: 231–236
11. Tutuncu AS, Faithful S, Lachmann B (1993) Intratracheal perfluorocarbon administration combined with mechanical ventilation in experimental respiratory distress syndrome: dose-dependent improvement of gas exchange. *Crit Care Med* 21: 962–969
12. Kirmse M, Fujino Y, Hess D, Kacmarek RM (1998) Positive end-expiratory pressure improves gas exchange and pulmonary mechanics during partial liquid ventilation. *Am J Respir Crit Care Med* 158: 1550–1556